Characteristic resistance curves of aortic valve substitutes facilitate individualized decision for a particular type

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Abstract

Objective: Biological valves exhibit characteristic curves (CC) regarding transvalvular gradient, resistance, and effective orifice area when correlated with a physiological cardiac output range (CO). The slope of the curve of transvalvular resistance over a typical CO range characterizes the clinical performance of the valve. These information may support an individualized decision towards the most adequate valve type. Methods: In an extracorporeal mock circuit two types of stented biological aortic valves (constructed pericardial valves, Edwards Perimount: EP; porcine cusp valves, Medtronic Mosaic: MM) of 21, 23, and 25 mm were investigated. Mean transvalvular gradient was measured over a range of 1.9 to 7.2 l/min CO at a simulated heart rate of 70 beats/min. Transvalvular resistance was calculated and presented as characteristic curves in a log-log-plot against cardiac output. Results: EP valves of all sizes demonstrated low slopes (resistance range; slope: 21 mm: 53–79 dynes s cm\textsuperscript{-5}; 0.29; 23 mm: 44–56 dynes s cm\textsuperscript{-5}; 0.12; 25 mm: 38–45 dynes s cm\textsuperscript{-5}; 0.12) while MM valves exhibited steep slopes (resistance range; slope: 21 mm: 46–169 dynes s cm\textsuperscript{-5}; 0.97; 23 mm: 36–146 dynes s cm\textsuperscript{-5}; 0.95; 25 mm: 27–64 dynes s cm\textsuperscript{-5}; 0.68) Conclusions: While constructed pericardial valves demonstrate sufficient hemodynamic performance especially in the higher CO range porcine cusp valves exhibited minor resistance in the lower CO range. Patients who exercise regularly may therefore profit from a pericardial valve while patients with a small body surface area and little exercise who therefore remain in the lower CO range may be adequately treated with a porcine cusp valve. 

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Keywords: Aortic valve; Biological valve replacement; Hemodynamics; Cardiovascular pathology; Cardiovascular model

1. Introduction

Demographic changes observed in western industrialized nations have inevitably resulted in an increase of age and morbidity of patients in need for aortic valve replacement [1]. As elder patients do exhibit a considerable susceptibility regarding cerebral or intestinal hemorrhage as well as bone injuries lifelong avoidance of anticoagulation has gained renewed interest [2]. As much evidence has been accumulated determining the average patency rates of biological valves to appear in the proximity of 10–12 years surgeons are increasingly inclined to offer biological valves to their elderly patients assuming that the life expectancy may very well match the patency of the prosthesis while offering a reasonable quality of life without the inherent risks of coumarin derivatives [3]. In the routine setting stented aortic valves appear to be preferably used because they facilitate and expedite implantation thereby reducing operative risks [4,5]. Interestingly, two entirely different types of stented biological valve substitutes have been engineered and refined in the last three decades. Valves constructed from bovine pericardium aligned on an artificial frame as well as porcine valves mounted on an artificial scaffold [6]. In numerous studies it has been shown that both valve types demonstrate a comparable clinical short and long term performance particularly in the aortic position [3,6–9]. Although pericardial valve substitutes tend to exhibit lower transvalvular gradients the assumed differential hydraulic behaviour has not yet been sufficiently and comprehensively revealed. It can be hypothesized that the particular hemodynamic properties which can be theoretically derived from the different engineering principles may very well account for a different in vivo behaviour [10]. It can even be speculated as to whether these differences may be utilized to match the particular hemodynamic advantages with the individual requirements of the patient while
diminishing the disadvantages of the particular design [11]. This study therefore intended to analyse flow-dependent hemodynamic parameters in a systematic fashion in order to derive characteristic resistance curves serving as decision tool towards an individualized indication for aortic valve replacement [10,13–15].

2. Materials and methods

2.1. Heart valve testing device and set-up

An established extracorporeal mock circuit designed for highly precise in-vitro measurements of the hemodynamic performance of heart valves and heart valve substitutes was utilized. The apparatus developed by Schichl and Affeld has been characterized in detail previously and is shown schematically in Fig. 1 [18]. Briefly, a piston-pump generated a constant stroke volume which was repeatedly ejected through the test valve. This process was controlled by a computer-driven programmable disk armature motor (F12M4, MATTKE AG, Freiburg, Germany) simulating a physiological aortic flow profile. After completion of the forward flow phase, the controller switched from flow control to pressure control so that a physiological diastolic pressure gradient was maintained by a computer-controlled retrograde motion of the piston. Upon termination of diastole, a new cardiac cycle was initiated in order to generate several consecutive beats by the device.

2.2. Parameter assessment and measuring protocol

Measurements during the first beat were discarded to attain a steady pulsatile state. In every experimental setting, measurements were conducted in 10 consecutive beats. The pressure difference across the valve were measured with two separate pressure transducers (PR 10, KELLER Ges. für Druckmesstechnik mbH, Jestetten, Germany). The amplification of one transducer was set according to the signal strength to achieve a higher resolution of the pressure signal during the systolic phase. The measurement of the piston displacement was accomplished with a digital angular transducer (GiO 40, TWK Messelektronik GmbH, Düsseldorf, Germany).

The results—flow and pressure difference—were given as curves (Fig. 2), and as tables with a resolution of 1 ms. The output diagram included the integrated data (see appendix): mean flow rate (MF; ml/s), root mean square flow (RMS; ml/s), stroke volume (SV; ml), simulated heart rate (HR; bpm), cardiac output (CO; l/min), mean pressure gradient (MTG; mmHg), closure time (CT; ms), closing volume (CV; ml), and leakage volume (LV; ml). Data were recorded in an electronic database for further processing. A dataset consisted of at least 12 different cardiac output measurements in order to assess the flow-dependency of EOA and TR of the respective study valve.

The precision of the parameters measured was as follows: volume ±1.0%, time ±1.5%, and pressure ±1.5%. The testing device enabled investigations over a broad spectrum of test parameters. Heart rate could be adjusted within a range of 30–150 beats/min with variable systolic ejection period (SEP; s/min). Stroke volume ranged from 30–100 ml while the pressure differences across the valve resembled the physiological systolic/diastolic values of 120/80 mmHg.

In this study and in accordance to the ISO and FDA standards for cardiac valve testing, measurements with aortic valves were carried out at a frequency of 70 beats/min and a SEP of 23.78 ± 0.11 s/min. Isotonic saline was used as the test fluid to achieve full transparency because it has been shown by us that fluid viscosity has only little influence on hemodynamic parameters obtained in ex-vivo mock circuits [21,22].

2.3. Data processing

Off-line analysis of the recorded data was performed using a self-developed software package. Full details of calculations and formulae were already provided in detail recently [21–23] (see Appendix A). Single cardiac cycles in every data set were mathematically combined to form an average beat which then served as a basis for all subsequent calculations.
2.4. Heart valve substitutes

Commercially available biological heart valve substitutes were used. Edwards Lifesciences Perimount Aortic Valves of 25, 23, 21 mm size (Edwards Lifesciences, Irvine, CA) and Medtronic Mosaic Aortic Valves of 25, 23, 21 mm size (Medtronic Inc., Minneapolis, MN). 19 mm valves were not investigated according to our clinical policy not to use 19 mm biological valve substitutes in adult patients.

2.5. Hemodynamic assessment and data acquisition

Transvalvular resistance (TR; dynes s cm⁻⁵) was calculated by 1333×MTG/MF. Effective orifice area (EOA; cm²) was calculated by \( \text{RMS}/(51.6 \times \text{MTG}^{1/3}) \) (see Appendix A).

The characteristic curves of a valve (CC) TR versus CO were plotted as log-log-plot in a CO-range of 1.5-7 l/min and linearized by a power function: TR = cCO^b. The weight factor c and the exponent β (the slope of the curve) were calculated by non-linear regression analysis ((c, β + SD) = rpg(log(\text{TR}); log(CO); true; true); Excel for Windows, statistic package, Microsoft Inc, Seattle, WA). Area utilization index (AI) related to the obturator area (AI-O) was assessed as: AI-O = 100EOA/OA (%); AI related to sewing ring area (AI-SR) (Performance Index acc. to Yoganathan [24]) was assessed as: AI-SR = 100EOA/sewing ring area (%).

2.6. Assessment of physical orifice dimension

The physical orifice diameter (POD; mm) of the respective valve type and size was measured with a Hegar obturator (diameter sizes: 16-31 mm; in 1 mm increments) while the outer diameter including the sewing ring was measured with a ruler. The obturator area (OA; cm²) was computed by: \( \pi(diameter/2)^2 \) (cm²).

2.7. Data acquisition and statistical analysis

All data were compiled by means of specifically designed software with a standard personal computer. Data were organized in a calculation sheet (Excel for Windows, Microsoft Inc, Seattle, WA). Descriptive and comparative statistical analysis were performed with standard software (SPSS for Windows). Flow independent parameters were analyzed using two-sided Student’s t-test in case of normal distribution or using Mann-Whitney test if non-normally distributed. Data are presented as mean values ± standard deviation (SD). Significant results were indicated at 5, 1, and 0.1% error level. *P<0.05; **P<0.01; ***P<0.001.

3. Results

3.1. Hydraulic valve parameters in the physiological range dependent on valve type and size

Mean transvalvular gradients (MTG) of the EP valves were typically lower than those of MM valves. The differences, however, diminished with increasing valve size. Regurgitation time (RT) of MM valves was shorter than that of EP valves. The differences increased with valve size.

3.2. Flow dependency of effective orifice area and resistance with respect to valve type and size

In general, a 2 mm larger obturator could be passed through the valve’s orifice in EP valves compared to MM valves of identical sewing ring size. Minimum computed EOA of MM valves was smaller than minimum computed EOA of EP valves while maximum EOA of EP valves was larger than maximum computed EOA of MM valves. The flow-dependent increase of EOA of the MM valve was 0 (21 and 23 mm) or low (25 mm) while the flow-dependent increase of EOA of EP valves of all sizes was significantly higher than 0. The flow-dependent increase of TR of the MM valve was 1 (21 and 23 mm) or 0.7 (25 mm) respectively, while the flow dependent increase of TR of EP valves of all sizes was significantly lower than 1. Small MM valves exhibited a flow-independent EOA whereas small EP valves demonstrated nearly flow-independent TR (Table 2).

Transvalvular resistance of all studied valves were plotted against cardiac output. Distinct slope differences of the two investigated valve types were observed which appeared to be rather independent of the valve size. MM valves showing an almost linear curve with steep slope while EP valves exhibited a non-linear curve with almost absent slope in the low CO range while exhibiting a steady increase of slope towards higher CO values (Fig. 3).

Table 1: Hydrodynamic valve parameters in the physiological normal range (HR: 70 bpm/CO: 4,9 l/min)

<table>
<thead>
<tr>
<th>Valve Type</th>
<th>MTG</th>
<th>CT</th>
<th>CV</th>
<th>LV</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP21</td>
<td>9.71±0.10</td>
<td>21±1.1**</td>
<td>−1.29±0.07***</td>
<td>−3.3±0.14***</td>
</tr>
<tr>
<td>MM21</td>
<td>15.5±0.72</td>
<td>19±1.0</td>
<td>−1.09±0.05</td>
<td>−1.0±0.04</td>
</tr>
<tr>
<td>EP23</td>
<td>7.46±0.08</td>
<td>32±1.4***</td>
<td>−2.15±0.11***</td>
<td>−2.7±0.16***</td>
</tr>
<tr>
<td>MM23</td>
<td>12.6±0.94</td>
<td>19±1.7</td>
<td>−1.13±0.08</td>
<td>−0.5±0.12</td>
</tr>
<tr>
<td>EP25</td>
<td>6.54±0.07</td>
<td>31±1.8***</td>
<td>−2.55±0.18***</td>
<td>−5.6±0.29***</td>
</tr>
<tr>
<td>MM25</td>
<td>7.30±0.06</td>
<td>22±1.7</td>
<td>−1.46±0.06</td>
<td>−0.9±0.14</td>
</tr>
</tbody>
</table>

PE, Edwards-Perimount Pericardial tissue valve; MM, Medtronic Mosaic Porcine cusp valve; MTG, Mean transvalvular gradient; RT, Regurgitation time; RV, Regurgitation volume; LV, leakage volume; statistical differences of the flow-independent parameters (CT, CV, LV) between the two study valves of the respective size are indicated as: **P=0.001; ***P<0.0001.

Regurgitation volume (RV) and leakage volume (LV) of MM valves were smaller than those of EP valves. Again, the differences increased with valve size (Table 1).

3.3. Area utilization index

In general, area utilization index related to the obturator area (AI-O) and area utilization index related to the sewing ring (AI-SR) increased with increasing flow. The increase of AI-O and AI-SR was higher in Edwards Perimount valves than in Medtronic Mosaic valves. Particularly the AI-O diminished in the same valve type with increasing size. Both, AI-O and AI-SR appeared to be advantageous in the low-flow range of the Medtronic Mosaic valve. The differences were most pronounced in small valves (21 mm). In contrast, AI-O and AI-SR were advantageous in Edwards Perimount valves of both smaller sizes (25 mm) in the high-flow-range (Table 3).
4. Discussion

During the last 15 years stented biological aortic valve substitutes have been investigated in an astounding number of publications [1–3, 6–8]. It was shown that both types of biological valves demonstrate reasonable hemodynamic performance in the clinical setting [1–3, 6]. It was also shown that the observed differences in transvalvular gradients were not followed by significant differences in left ventricular remodelling as well as clinical outcome [7]. Instead, evidence was accumulated that left ventricular muscle mass regression as one of the key indicators for adequate clinical recovery of the heart did not differ significantly [20, 16–17]. Investigations, however, further revealed that degeneration of biological valves appeared after a typical time frame of 8–15 years notwithstanding the particular valve type [3]. Fortunately, it was also demonstrated that elderly patients fared reasonably well with biological valves in terms of longevity and quality of life [6, 7]. A paucity of evidence, however, has been provided, regarding a potentially different clinical behaviour of both valve types when looking at the individual situation of a patient [1, 2]. The transvalvular gradient appeared almost exclusively in a variety of publications as a tool towards a differential decision. It was assumed that patients with a small annulus require a valve with the largest effective orifice area available for a given size [6, 8]. As pericardial valves showed smaller transvalvular gradients when compared to porcine valves of the same size pericardial tissue valves were often proposed as the substitute of choice in an annulus of limited dimensions [5]. This, however, may be a superficial attitude. Already in 1978 Rahimtoola had inaugurated the concept of patient-prosthesis mismatch as one of the key factors for appropriate prosthesis selection [24]. Dumesnil could later show that a small decrease in the effective orifice indexed for body surface area was accompanied by large increments of transvalvular pressure gradient when looking at the increase of stroke volume during exercise. From his ex-vivo investigations he recommended the indexed effective orifice area to be not less than 0.9–1.0 cm²/m² for aortic prostheses [25]. The concept of effective orifice area index being the clinical equivalent for the behaviour of a valve of too small a size over the entire range of exertion the patient generates, however, has been heavily debated over the following years. While proponents repeatedly advocated to abide by this threshold the majority of clinical investigations could demonstrate that small prosthesis can indeed be implanted and that patient-prosthesis mismatch does not play as much a clinical role.

Table 2
Flow-dependency of EOA and TR. Flow-range of 1.5–7 l/min compared to the physical orifice area. Values and slope of linearized CC in log-log-plot

<table>
<thead>
<tr>
<th>Obturator</th>
<th>EOA</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Min</td>
<td>Max</td>
</tr>
<tr>
<td>EP21</td>
<td>18</td>
<td>2.54</td>
</tr>
<tr>
<td>MM21</td>
<td>16</td>
<td>2.01</td>
</tr>
<tr>
<td>EP23</td>
<td>20</td>
<td>3.14</td>
</tr>
<tr>
<td>MM23</td>
<td>18</td>
<td>2.54</td>
</tr>
<tr>
<td>EP25</td>
<td>22</td>
<td>3.80</td>
</tr>
<tr>
<td>MM25</td>
<td>20</td>
<td>3.14</td>
</tr>
</tbody>
</table>

D, obturator diameter; A, obturator area; EOA, effective orifice area; EP, Edwards-Perimount Pericardial tissue valve; MM, Medtronic Mosaic Porcine cusp valve.

Fig. 3. Flow-dependence of transvalvular resistance: Transvalvular resistance of all study valves is plotted against cardiac output. Note the distinct slope differences of the two investigated valve types independent of the valve size. EP valves showing an almost linear curve with steep slope while MM valves exhibit a non-linear curve with absent slope in the low CO range while exhibiting a steady increase of slope towards higher CO values.
as assumed [6,7,9,12,19]. Small valves are not necessarily bad as demonstrated by Medailon and others [4,5,8]. The current perception of patient-prosthesis mismatch may thus be reconsidered at least for selected patient cohorts as quoted by Freed and coworkers [16].

In our study we therefore looked at the hydraulic properties of biological aortic valves over a typical and physiological range of cardiac output. We were able to prove the data in the literature and could demonstrate that pericardial valves indeed exhibit lower transvalvular gradients because of the larger effective orifice area [11]. We could furthermore support the data in the literature regarding the opening and closure characteristics of Medtronic Mosaic and Edwards Perimount valves [3]. However, in our study it became evident that the behaviour of the effective orifice area, which resembles the opening and closure characteristics of the different types of biological valves was responsible for a flow dependent hemodynamic performance [13–15]. By means of a resistance/CO log-log-plot distinct slope differences were visualized showing differential behaviour of both valve types independent of the size. Our study indicated that the effective orifice area of pericardial valves is flow-dependent. This indicates that the valve does not open entirely under low-flow conditions while it can adapt to a wider cardiac output range by an effective orifice area increase. In contrast, porcine cusp valves exhibit the entire effective opening of the valve already under low-flow conditions while not showing a cardiac output dependent effective opening area reserve. The different characteristics of the valves allow therefore for an individualized choice of valve type: Patients, in whom CO-ranges in the proximity of 3-6 l/min can be assumed, may be candidates for porcine cusp valves while patients exhibiting a larger CO range between 4-10 l/min may consequently be candidates for pericardial valves. It was demonstrated that Medtronic Mosaic valves appear to be particularly advantageous in the smaller range of cardiac output while our data indicated that Edwards Perimount valves appear to be advantageous in the higher CO range.

4.1. Limitations of the study

Artificial models offer a wide spectrum of experimental settings while providing accurate data. Furthermore, they can reduce the number of animal experiments. However, the transfer to the in-vivo situation is limited. Aspects of the central and peripheral circulation, such as the ‘Windkessel’ effect play a major role in valve behaviour but are only simulated in our model. The outflow tract of our model is straight and not naturally curved. As a consequence, the in vivo hydraulic behaviour of a valve may differ from our idealized assumptions. Furthermore, an altered configuration of the subvalvular left-ventricular outflow tract due to the implantation procedure itself was not simulated. Isotonic saline was used in our model. In contrast, blood is a Non-Newtonian fluid exhibiting velocity dependent viscosity. Instead of blood one can utilize 30% glycerol solution which resembles the viscosity of blood. However, Werner has already demonstrated that the fluid viscosity has little influence on systolic valve parameters. By using 0.9% saline, however, pressure gradients may be slightly underestimated and leakage volumes overestimated [21,22]. Most certainly, our in vitro study can provide but first insights into the assumed potential of biological valves regarding a differential indication. In vivo studies are required to verify our initial findings and theoretical assumptions. Other biological valves fabricated with pericardial tissue or assembled from porcine aortic valves may exhibit different properties. Although not yet proven, we however, believe that our findings may perhaps have exemplary character regarding both main constructive types.

4.2. Conclusion

In the clinical scenario rather small and fragile elderly patients who may exhibit a cardiac output of hardly more than 3 l while sleeping and who do live with only moderate exertion may be best served with a porcine cusp aortic valve while elderly individuals of larger size and weight who perform demanding exercise on a regular basis such as biking or hiking may profit from a pericardial aortic valve. Characteristic curves have the potential to supplement the indexed effective orifice area (EOA) for verification of patient-prosthesis mismatch or -in other words- to predict proper patient-prosthesis match.

References


Appendix A. List of abbreviations, symbols, and the formula used (Fig. 2)

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
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<tbody>
<tr>
<td>SV</td>
<td>stroke volume (mL)</td>
</tr>
<tr>
<td>CO</td>
<td>cardiac output (L/min)</td>
</tr>
<tr>
<td>ΔP(t)/MTG</td>
<td>instantaneous systolic pressure drop/mean transvalvular gradient (mmHg)</td>
</tr>
<tr>
<td>EOA</td>
<td>‘effective orifice area’ (cm²)</td>
</tr>
<tr>
<td>ET/CT/DFP</td>
<td>ejection time/time to close of the valve/diastolic filling period (ms)</td>
</tr>
<tr>
<td>HR</td>
<td>heart rate (min⁻¹)</td>
</tr>
<tr>
<td>SEP</td>
<td>systolic ejection period (s/min)</td>
</tr>
<tr>
<td>CV</td>
<td>closing volume (mL)</td>
</tr>
<tr>
<td>LV</td>
<td>leakage volume (mL)</td>
</tr>
<tr>
<td>ρ</td>
<td>density of the fluid (g/ml)</td>
</tr>
</tbody>
</table>

\[ \text{mean flow rate } MF, \text{ root mean square-flow RMS, stroke volume } SV, \text{ and cardiac output } CO: \]
\[ \text{MF} = \frac{1}{ET} \int_{0}^{ET} Q(t) \, dt \]
\[ \text{RMS} = \sqrt{\frac{1}{ET} \int_{0}^{ET} Q(t)^2 \, dt} \]
\[ \text{SV} = \frac{ET \cdot CO}{HRSV \times 1000} \]
\[ \text{CV closure volume } CV, \text{ leakage volume } LV: \]
\[ \text{CV} = \int_{0}^{ET} Q(t) \, dt \]
\[ \text{LV} = \frac{Q(ET)}{ET} \]
\[ \text{mean transvalvular gradient } MTG, \text{ transvalvular resistance } TR, \text{ and effective orifice area } EOA: \]
\[ \text{MTG} = \frac{1}{ET} \int_{0}^{ET} \Delta p(t) \, dt \]
\[ TR = 1333 \frac{MTG}{MF} \]
\[ EOA = \frac{RMS}{MTG/ρ} \]

Appendix B. Conference discussion

Dr. H. Vanermen (Aalst, Belgium): I’ve got a question about your conclusions. Old ladies, most of the time, have very small annuluses. So most of the time we have the tendency to pick up a valve that’s got better hemodynamic performances even at high cardiac outputs because most elderly people now are getting more and more active, too.

Dr. Kuehnel: The small annulus diameter with old ladies is a point of interest, but I think then the gradients shows us that the Medtronic valves in the lower flows are better. In other studies, also, the small sizes you need in this situation take good results.

Dr. Vanermen: One may anticipate more calcification to develop in the porcine valves versus the pericardial valves as well.

Dr. Kuehnel: Yes. This is an in vitro study following hemodynamic parameters. It is not only one point. We have a discussion picture and you can see here, this is from unpublished data from another study, you can see here the pericardial valve and the Medtronic Mosaic valve. And you can see here under low-flow condition the pericardial valve opens only a little bit and here it opens greater. And this could be a reason for calcification, yes.

Dr. Vanermen: It’s a very interesting finding.

Dr. A. Wechsler (Philadelphia, PA, USA): Did you measure the orifice area of each valve?

Dr. Kuehnel: Yes, we measured with a Hegar probe; and we visualized this and can planimeterate this area also.

Dr. Wechsler: And did you find that a 21 is exactly 21?

Dr. Kuehnel: Yes. The Medtronic Mosaic are 1 mm diameter lower than the pericardial valve each size.